بسم الله الرحمن الرحيم

Glucose Metabolism: Gluconeogenesis

By

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Objectives

- The importance of gluconeogenesis as an important pathway for glucose production
- The main reactions of gluconeogenesis
- The rate-limiting enzymes of gluconeogenesis
- Gluconeogensis is an energy-consuming, anabolic pathway

Gluconeogenesis: An Overview

- Liver (mainly) and Kidneys
- Both mitochondria and Cytosol

  Exception: Glycerol, only cytosol
- Gluconeogenic substrates:

  Glycerol

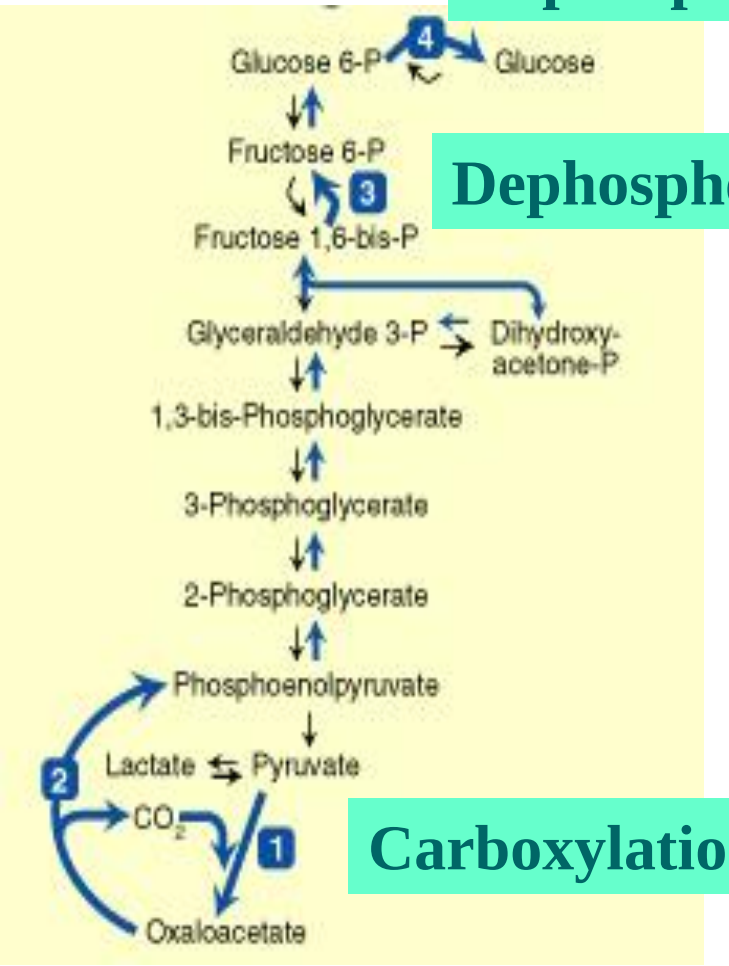
  Lactate and Pyruvate

  Glucogenic amino acids

Gluconeogenic Pathway

Dephosphorylation of G-6-P

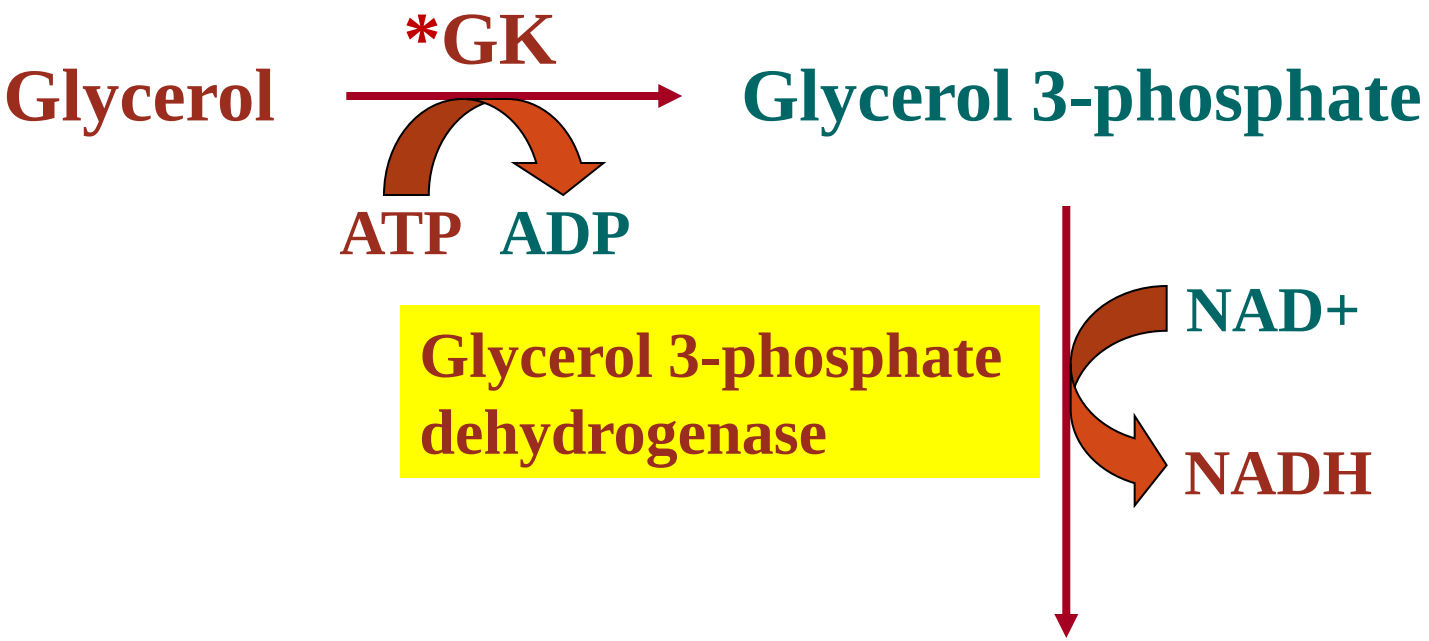
Dephosphorylation of F 1,6-P



Transport of OAA & decarboxylation into PEP

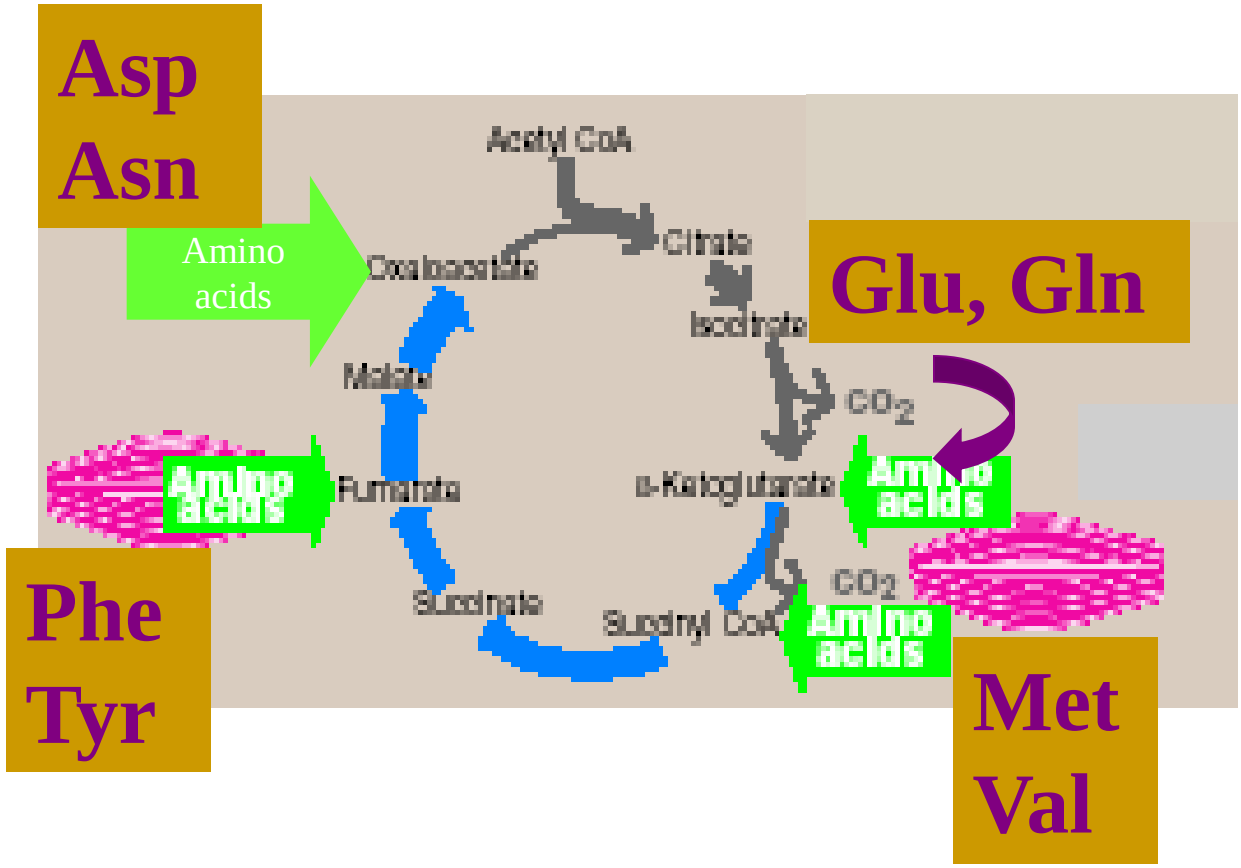
Carboxylation of pyruvate

Gluconeogenic Substrates: Glycerol

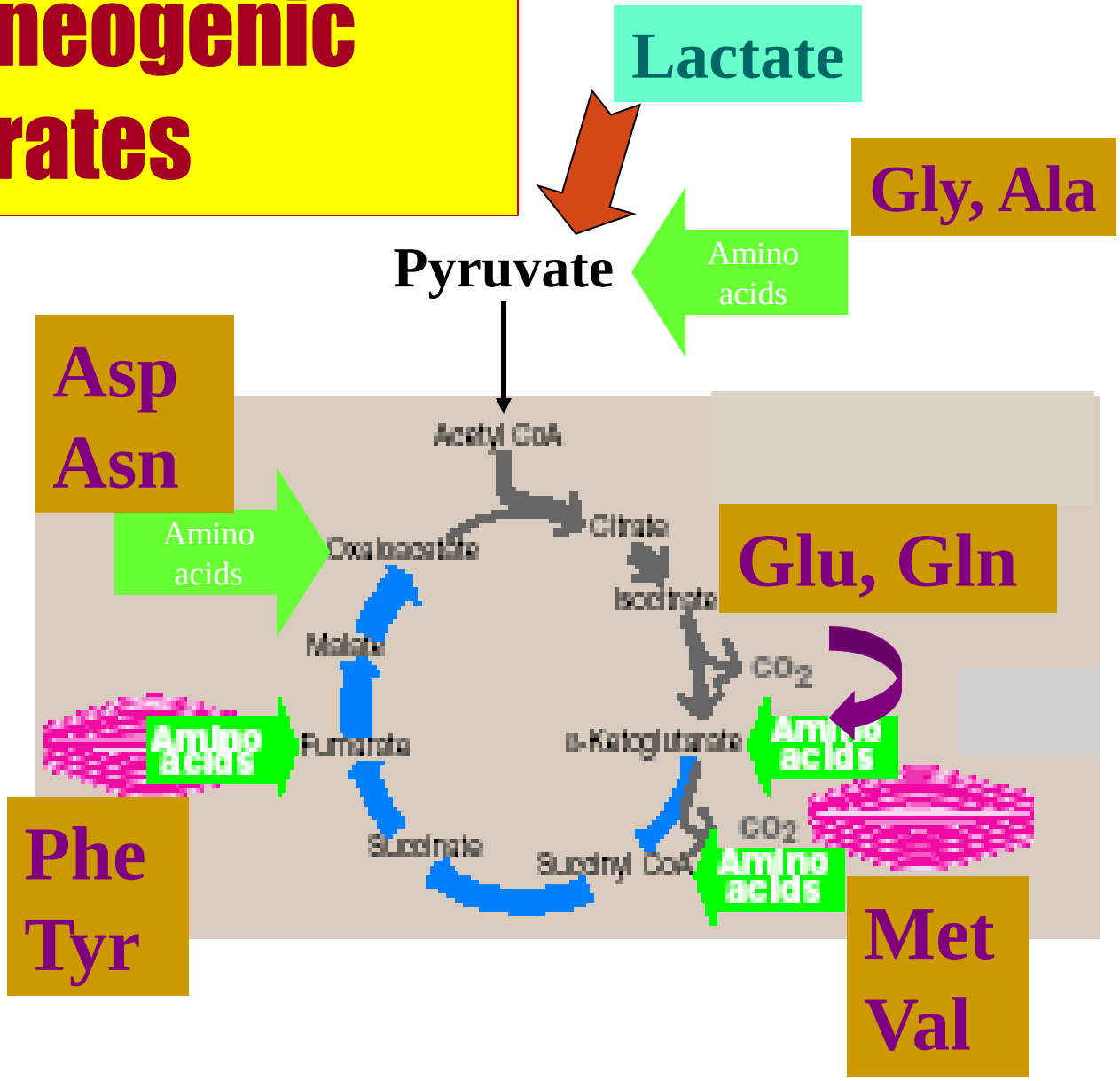


*GK: Glycerol kinase only in liver & kidneys

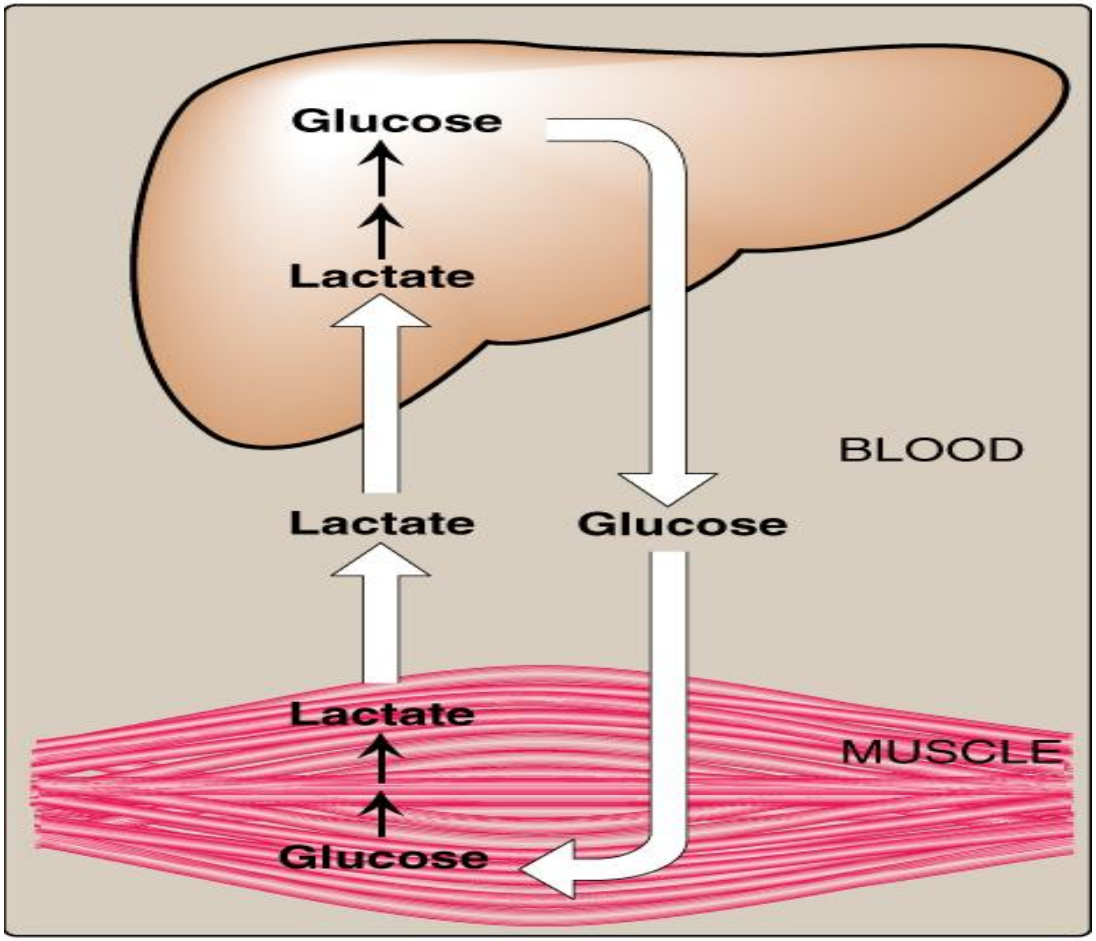
Glucogenic Amino Acids



Gluconeogenic Substrates



Gluconeogenic Substrates: Lactate (Cori Cycle)



Gluconeogenic Pathway

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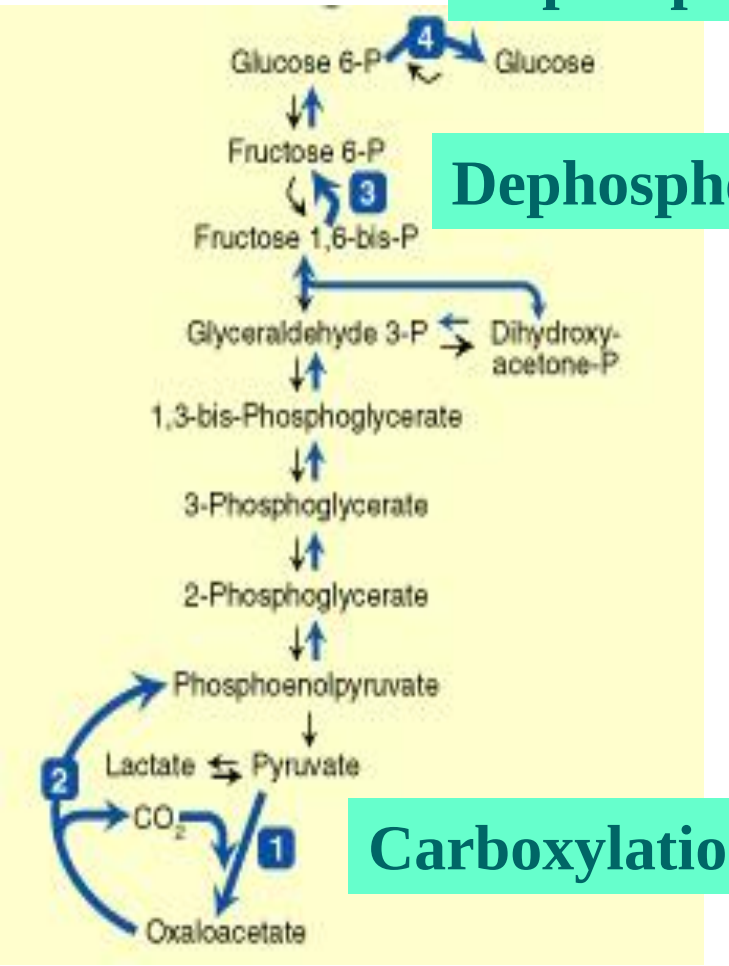
Dephosphorylation of F 1,6-P



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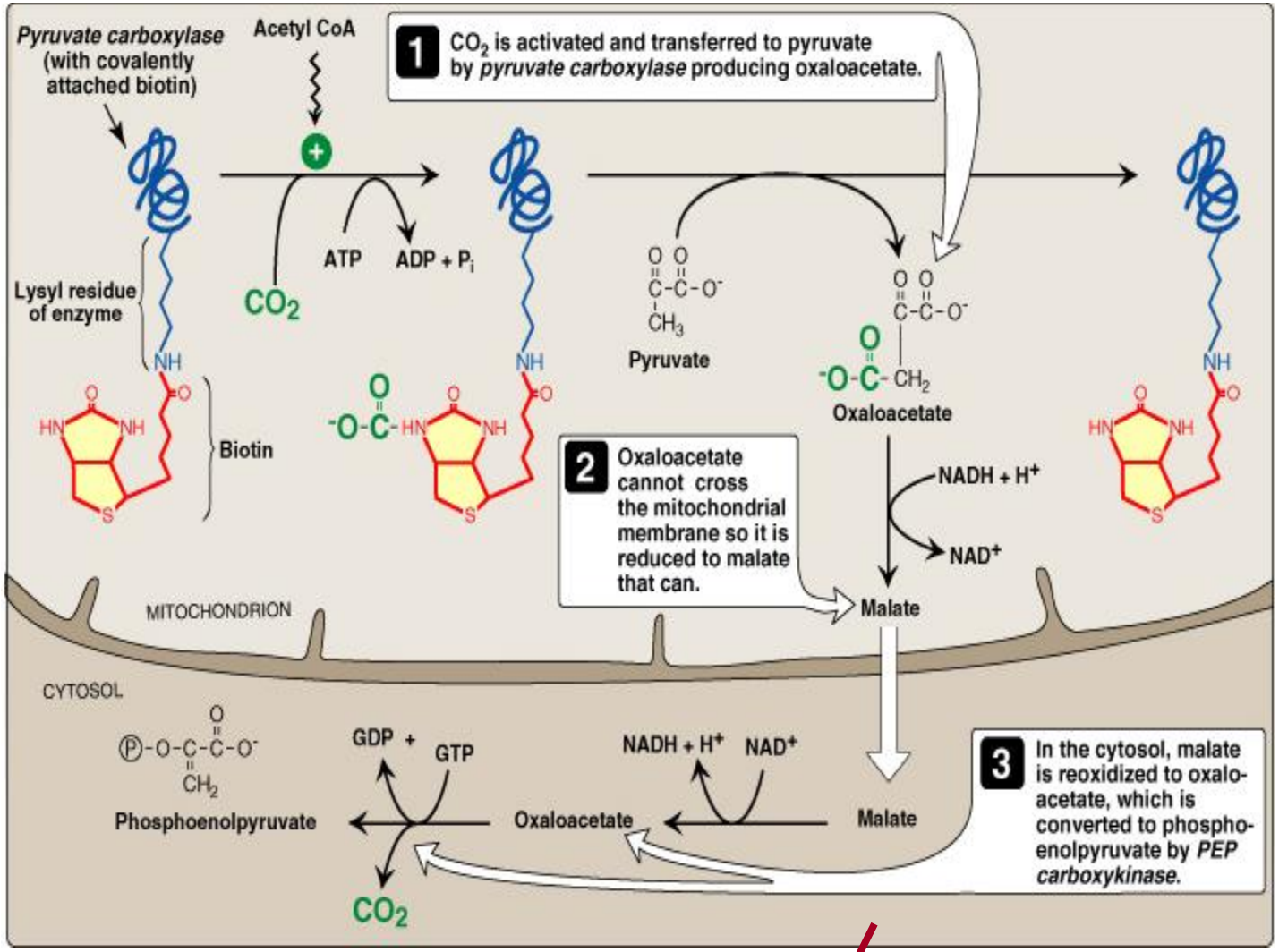
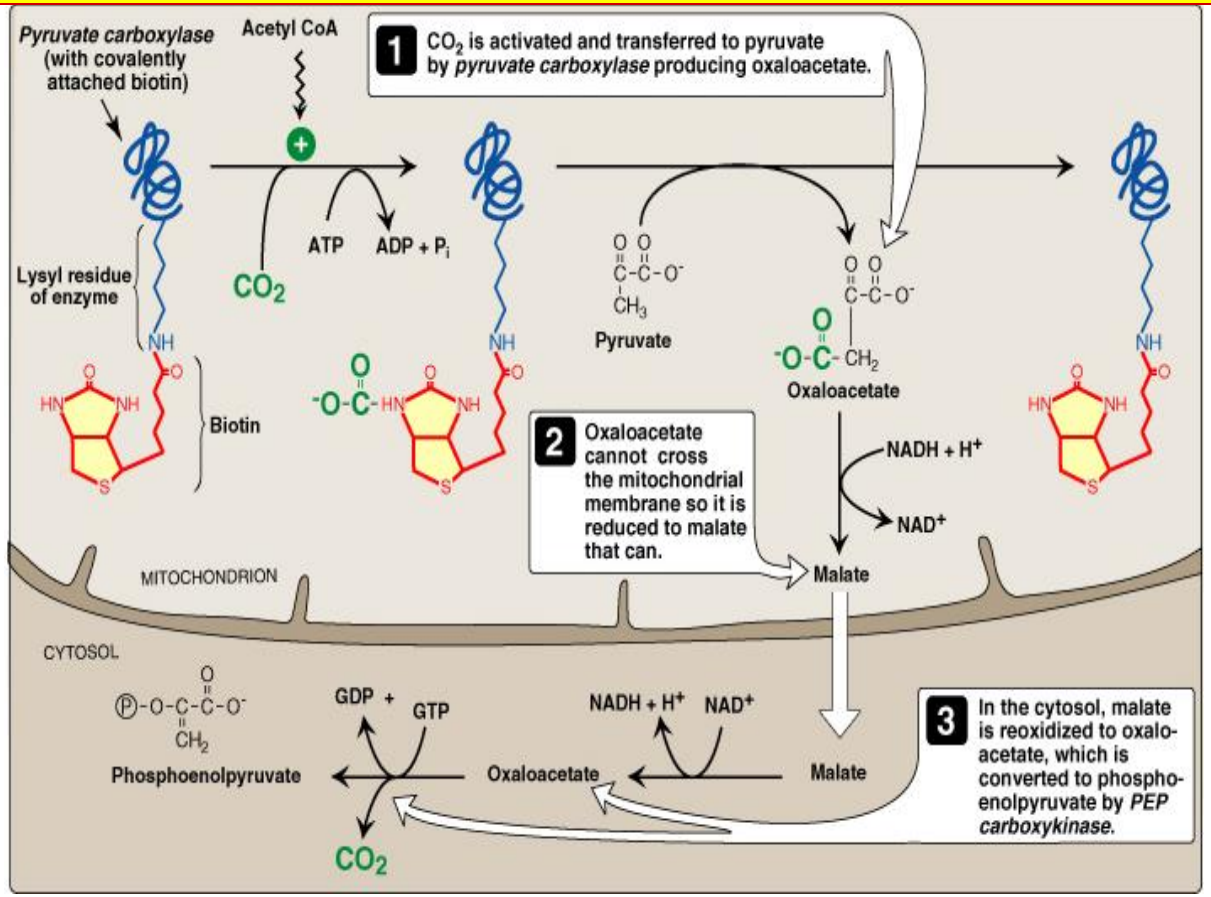
Carboxylation of pyruvate

Pruvate Carboxylase and PEP-CK



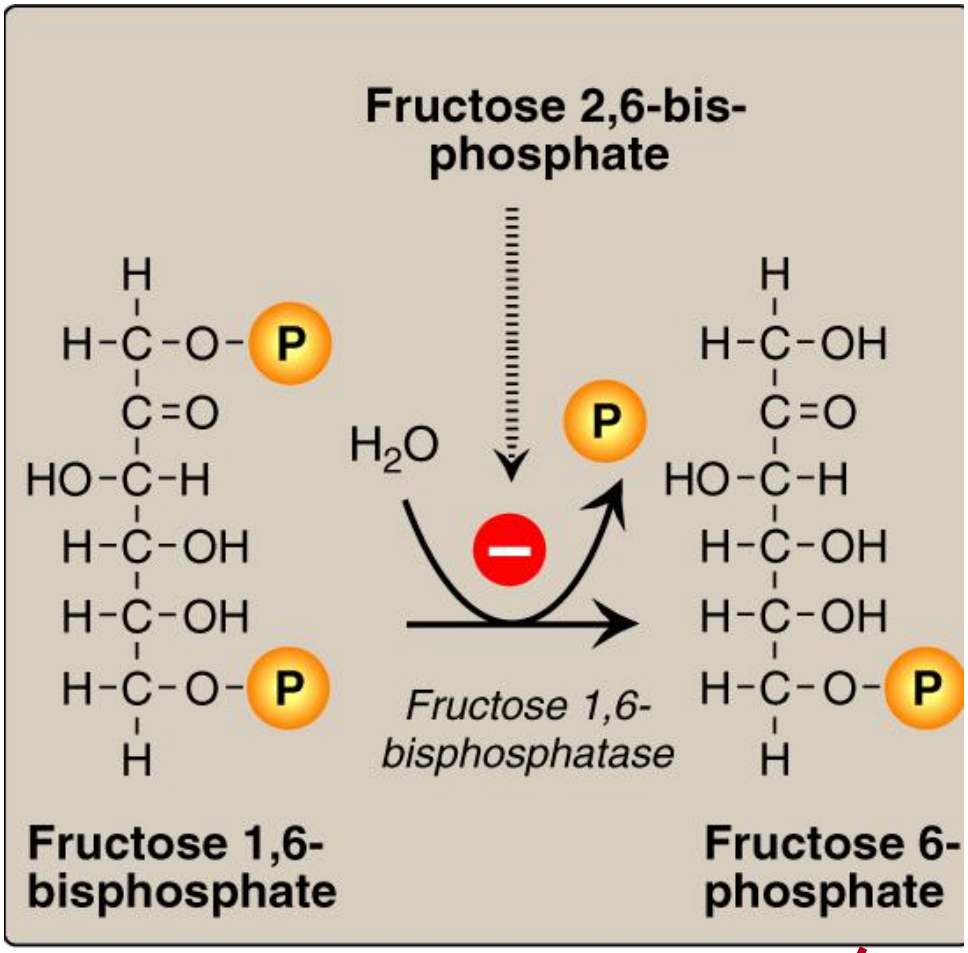
Pyruvate carboxylase + PEP-CK ≠ Pyruvate kinase

Regulation of Pruvate Carboxylase



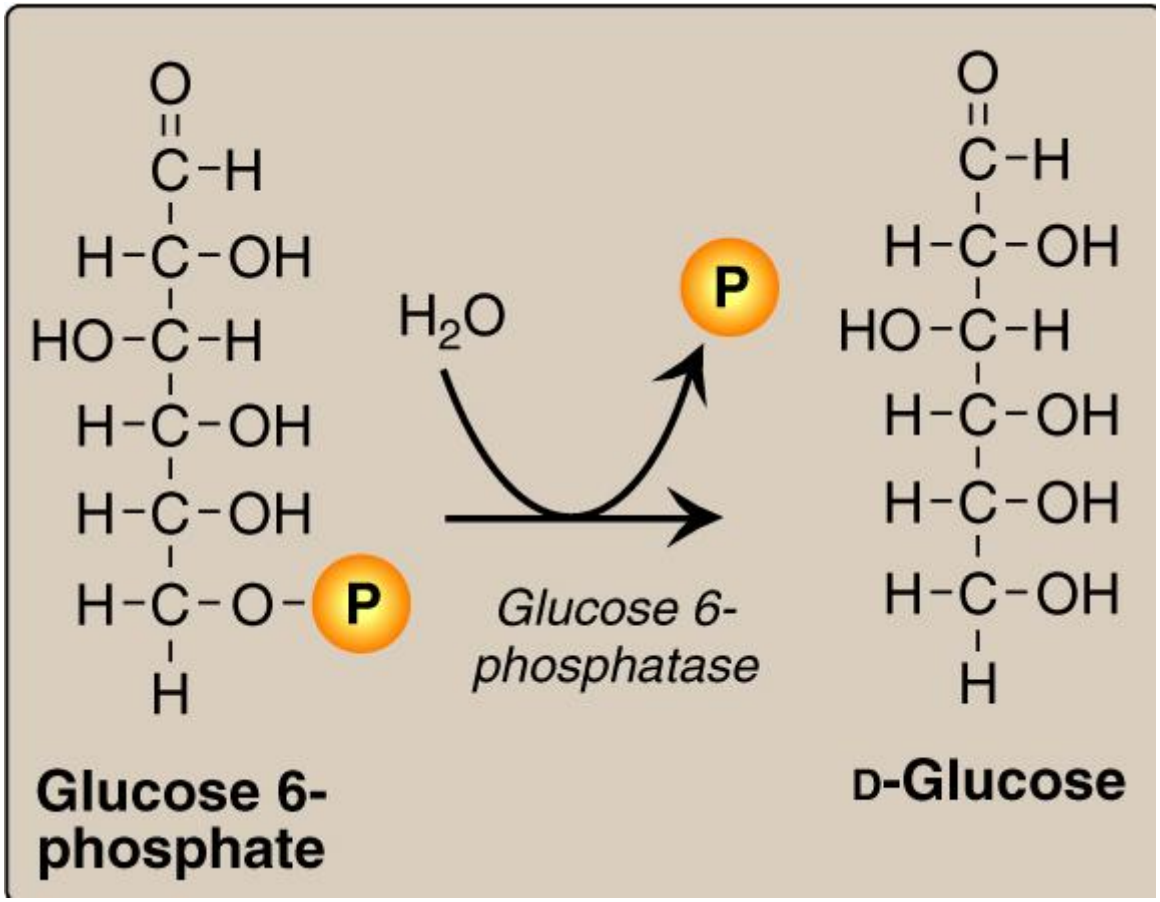
Fasting → ↑lipolysis in adipose tissue → ↑ FFA to liver → FA oxidation → ↑Acetyl CoA → allosteric activation of pyruvate carboxylase to increase the Gluconeogensis rate

Fructose 1,6-Bisphosphatase



Fructose 1,6-bisphosphatase ≠ PFK-1

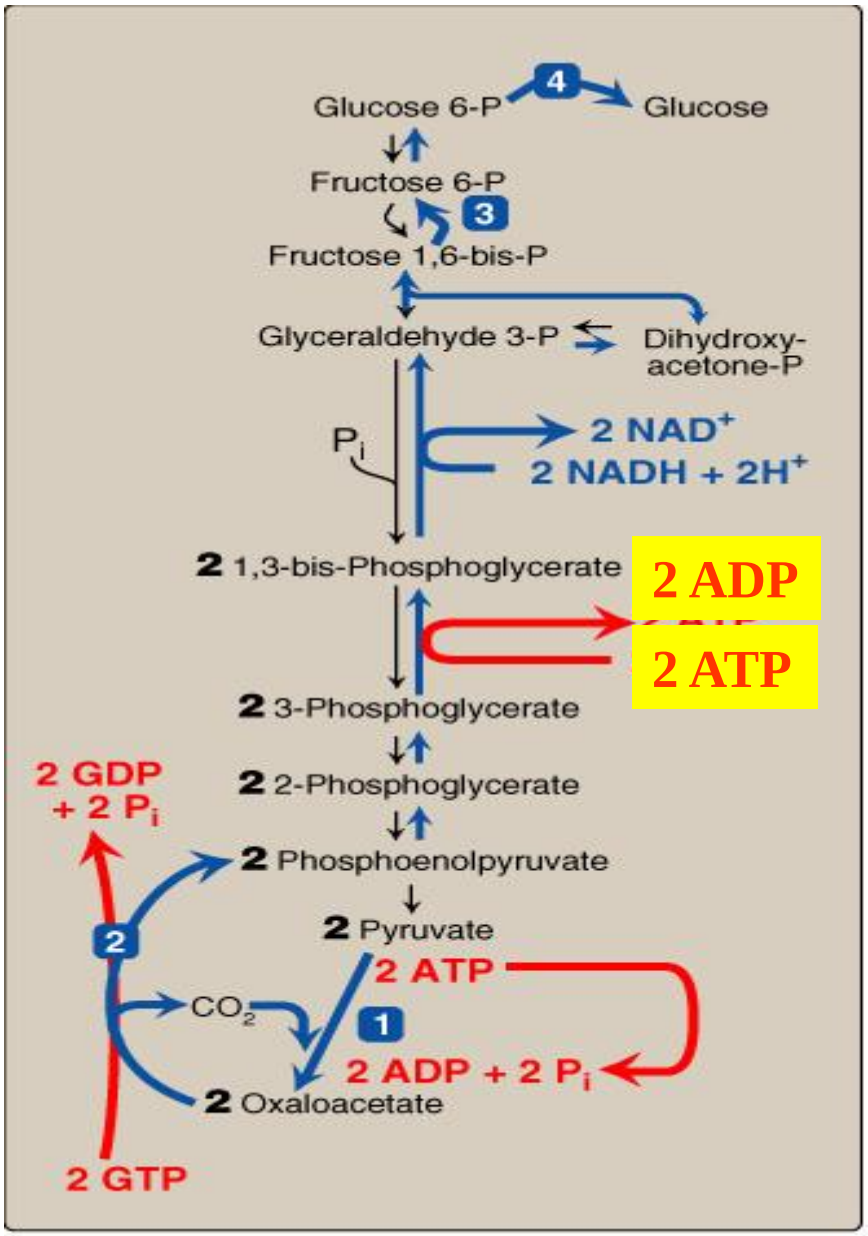
Glucose 6-Phosphatase



Glucose 6-phosphatase ≠ Glucokinase

Gluconeogensis: Energy Consumed

Six High-Energy Phosphate Bonds From Pyruvate to Glucose



Gluconeogenesis: Regulation

- **Reciprocal control**

  Gluconeogenesis & Glycolysis

- **Allosteric:**

  ↑Acetyl CoA → stimulates Pyruvate carboxylase

  ↓ AMP or ↑ ATP
  (i.e. energy-rich state in cells)
  ↓ F 2,6-Bisphosphate
  } **→ Stimulate F 1,6-bisphosphatase**

- **↑Glucagon (or ↓ I/G ratio): stimulates gluconeogenesis**

  Allosteric (glucagon → ↓ F 2,6-Bisphosphate)

  Induction (glucagon → induction of PEP-CK gene)

Take Home Message

- Gluconeogenesis:
  - Synthesis of glucose from noncarbohydrates
  - Anabolic
  - Energy-consuming
- 4 Unique enzymes are required for reversal of the 3 irreversible reactions of glycolysis
- Both gluconeogenesis & glycolysis are reciprocally-regulated